Improving MEDication Adherence through Person Centered Care and Adaptive Interventions (iMedA)

Solution

This project will improve medication adherence (MA) for hypertensive patients through an AI agent that supports doctor and patient in collaboratively understanding key individual adherence risk factors and designing an appropriate intervention plan. iMedA will then deliver the selected intervention through a mobile App and follow-up on its effectiveness in order to, over time, improve the system. The combination of person-centered care and self-management interventions will lead to significantly improved health outcomes and reduced healthcare costs.

The incidence of hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) in Sweden is estimated at approximately 27%[1]. Among American adults diagnosed with hypertension only 54% had their condition under control; another 32% had prehypertension-level blood pressure. The direct and indirect healthcare costs due to uncontrolled hypertension in US alone are estimated at 49 billion dollars each year[2]. It is a major risk factor for coronary heart disease and stroke as well as heart failure. MA is a key factor for good clinical outcomes in hypertensive patients.[3] However, medication non-adherence in this group is very high, especially for newly diagnosed patients. A British study reported antihypertensive drug discontinuation rates of 20.3% at 6 months and 28.5% at one year[4]. All this makes hypertension a good model disease in conceptualising the project.

There is evidence that MA and medical outcomes improve when care is a collaborative effort between patients and healthcare providers.[5] Sweden is already a leading country in implementing a system-wide paradigm shift towards person-centered care (PCC). iMedA aims to propel PCC by implementing and deploying in Region Halland (RH) a new decision support system based on state-of-the-art AI techniques. It empowers hypertensive patients to take more responsibility for their health through self-management solutions, and provides doctors with the information they need to offer more PCC. Those main aspects will be brought together using three AI techniques: information fusion and representation learning to create comprehensive descriptions of patients; peer group based interpretable machine learning to predict non-adherence; analysis of causal chaining and confluence to identify individually appropriate interventions. iMedA project partners have the combination of expertise and resources to address all the critical aspects necessary for the success of the project: the technical, medical, and organisational challenges.

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[1] SBU. Moderately elevated blood pressure. Stockholm: Swedish Council on Health Technology Assessment in Health Care (SBU); 2007. SBU report no 170 (in Swedish).

[2] R. Merai, et al. "CDC Grand Rounds: A Public Health Approach to Detect and Control Hypertension." MMWR Morb Mortal Wkly Rep. 2016 Nov 18;65(45):1261-1264

[3] M. Krousel-Wood, et al. "Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients." *Current opinion in cardiology* 19.4 (2004): 357-362.

[4] T. A. Burke,, et al. "Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice." *Journal of hypertension* 24.6 (2006): 1193-1200.

[5] B. Södergård. "Adherence to treatment: what is done in Sweden? Practice, education and research."

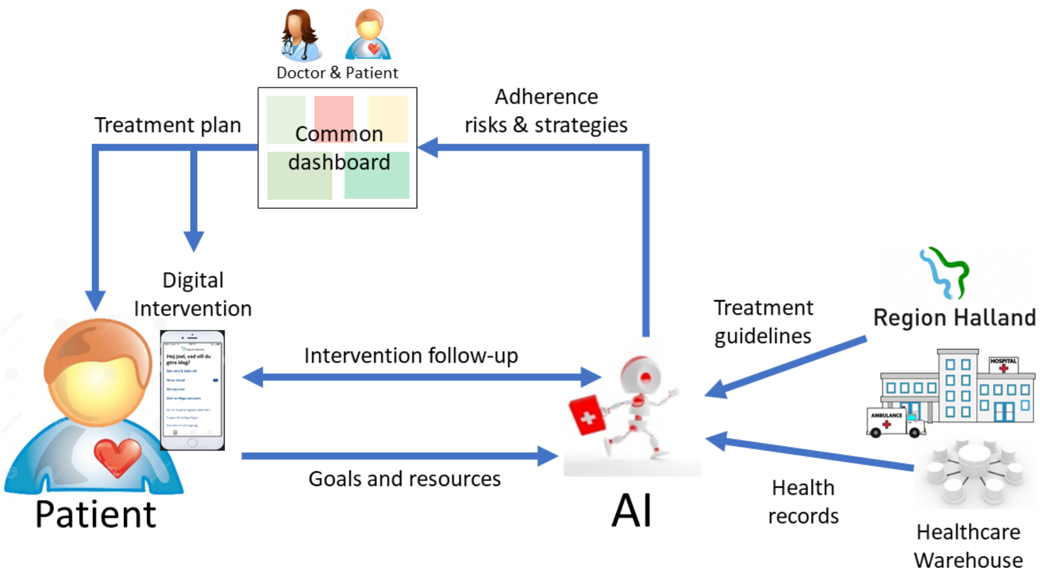

Figure 1. iMedA helps doctors and patients achieve higher treatment concordance.

In order to identify adherence risk factors and suggest adequate intervention strategies for individual hypertensive patients, the system must take into account health records as well as self-reported input from the patient. The AI agent's role is to understand how both medical and personal factors interact with respect to MA. Once key risk factors are identified, the AI agent can suggest appropriate intervention strategies. This information is displayed on a "dashboard" that guides a conversation between patient and doctor. Together, patient and doctor can agree on a treatment plan and interventions to be delivered via a mobile phone App. Interventions may include reminders, educational content and behavioural change strategies, among others. The AI monitors the effectiveness of interventions in order to optimize interventions and improve its decision support over time.

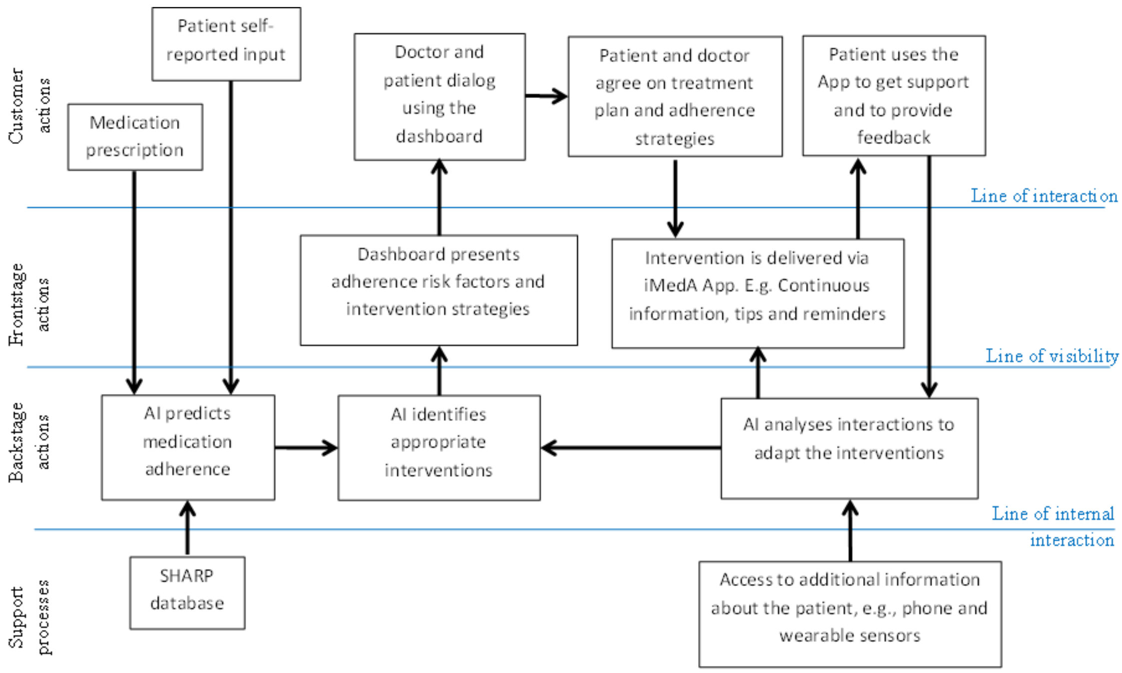

Figure 2. Service Blueprint for iMedA describing interactions with users

The interactions between users and iMedA follow the service blueprint illustrated in Figure 2. The front stage actions include the dashboard, which guides patient-doctor interaction; and an intervention App, which supports the patient at home. The main benefits come from supporting both PCC strategies and the work-flow for healthcare personnel, and from providing continuous and adaptive self-management support for the patients. Both have been shown to improve MA. When combined, these complementary approaches will significantly increase hypertension medication adherence.

Actors

Halmstad University (HU)
The Center for Applied Intelligent Systems Research (CAISR) at Halmstad University has considerable expertise in AI, in particular, machine learning and data mining. CAISR has a long history of collaboration with industrial partners on practical implementations of state-of-the-art solutions. CAISR is involved in several health technology projects with both national and international collaborators. CAISR will deliver the AI agent for iMedA.
The Centre of Research on Welfare Health and Sports (CVHI) at Halmstad University is a multi-disciplinary team of researchers from medical science, nursing, public health, sociology and psychology. The centre has a strong track record of research on development, validation and implementation of health innovations, in collaboration with stakeholders from the public sector and user groups. CVHI will lead study design and outcome evaluation of iMedA.

Region Halland (RH)
RH is the requirement owner for this project. In particular, Halland's Hospital (HH) aims to improve patient outcomes and reduce costs by increasing MA. The project group includes specialist doctors and high-level managers. HH will arrange the recruitment of patients and carry out the clinical study.
The Avdelningen för Kvalitet inom hälso- och Sjukvård (KHS) is tasked with ensuring the best possible care for all Halland residents. One of their key responsibilities is the compilation of guidelines and best practices for medication prescription. KHS will ensure iMedA follows those guidelines.
Digital Lab (DL) initiative focuses on improving digital user experience for Halland residents interacting with public institutions and services, e.g., healthcare. The team of programmers and service designers builds digital experiences such as websites and apps. DL will create iMedA digital user interface and integrate into RH digital platform.

Affecto (AF)
Affecto Sweden AB currently provides IT services and infrastructure for RH, which makes use of a considerable amount of data from different parts of the healthcare system. AF's business model revolves around "combining information with insight," with iMedA adding considerable value to this portfolio. Affecto will integrate iMedA with the existing IT infrastructure.

Artificial intelligence (AI)

Three main AI approaches will be integrated to build the complete iMedA agent:

1) To create a meaningful and comprehensive representation of each patient we will utilise *information fusion* and *representation learning* techniques. The data available for each patient in the system is of very high dimensionality; some of it structured and a lot unstructured. Combining all this information into a succinct representation is a difficult task. Today there is no clear consensus on which factors are relevant and what facts about the patient need to be considered. An additional challenge comes from the need for descriptions that can be visualized and understood by humans: both clinicians and patients themselves. From the field of information fusion, we will primarily focus on object assessment and situation assessment techniques, however, we need to consider all three relations between data sources: complementary, redundant and cooperative. The nature of the information is mainly "data-in-feature-out" and "feature-in-decision-out" levels. For representation learning, the goal is to replace manual feature engineering with both supervised (dictionary learning) and unsupervised (local linear and nonlinear embedding) approaches. In particular, deep neural networks have recently been used with great success for representation learning in many domains, including healthcare.

2) To predict non-adherence for concrete patients we will use *interpretable supervised machine learning* methods. Available data on medication prescriptions and pharmacy pickups will be used for training the model which determines, for each individual, the degree and likelihood of non-adherence. However, MA depends on many complex factors and black-box predictions are not enough to select interventions. It is important that the results produced by the predictive model are understandable and provide relevant insight into the factors that were individually most influential[6]. To this end, we will combine machine learning with *peer group analysis*. By identifying groups of similar patients, we can make inferences from the collective behaviour, and use them to inform choices for each individual separately. Here, the definition of "similar" is a challenge, since two patients may be similar regarding their medical condition and treatment, but not similar regarding behavioural factors; or vice versa. Groups will be identified using clustering and anomaly detection methods, as well as based on surveys and feedback data collected through iMedA App.

3) To identify a selection of intervention strategies that are the most appropriate for a particular patient we will use both *data-driven* and *knowledge-driven* approaches. The iMedA solution will combine both the expert medical knowledge from project partners with the data mining insights from regional data and other data sources. In particular, we will base the suggestions on the recommendations given for the patient group, together with the predictive factors identified as the most important ones for each individual. An analysis of causal chaining and confluence among those factors will be performed, and results will be presented so that clinician and patient together can design the best intervention. There is considerable literature describing effective intervention strategies for different patient groups[7]. iMedA will help doctors and patients select an appropriate combination of them from an evidence-based list. An "explanation" of why these options were selected as best matches in each case is crucial to achieve acceptance for the system, and also to guide meaningful dialog between patient and doctor.

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[6] Workshop on Human Interpretability in Machine Learning at ICML, Sydney, Australia, August 2017.

[7] EC. Morrisseya et. al. "Effectiveness & content analysis of interventions to enhance medication adherence & blood pressure control in hypertension: systematic review & meta-analysis." *Psychol Health*

The AI agent will be created by CAISR, whose mission is to promote the development of industry and society through research on Machine Learning and Data Mining methods that are suitable for solving relevant, real-life problems. The researchers involved in iMedA have a successful track record of doing AI projects across disciplines, with over 20 finished and almost 10 running projects of varying sizes (total grants for CAISR of over 35 MSEK with total project budgets of almost 100 MSEK).

Regulatory issues

The iMedA AI agent will be implemented as part of the existing IT infrastructure at RH, which already abides by data protection legislation and regulatory issues. The main addition to the current IT infrastructure is the iMedA App that will deliver different interventions to support self-management of patients at home. The regulations on Health Apps are unclear at the moment. However, the The Medical Device Directive 93/42/EEC (MDD) explicitly includes in the definition of medical device any software intended for diagnostic and/or therapeutic purposes. Given the increasing popularity of Health Apps, we believe this directive will soon be enforced on Apps as well, thus we intend to make iMedA App compliant with all the requirements for a Class I medical device so that a CE mark may be easily acquired before commercialization of the App.

Integrity aspects

In order to undertake this study, we will obtain ethical approval from the regional board of ethics in Lund. A nearby project has previously been approved on the same data. Participants will be recruited to the study through existing channels at RH (e.g., by their physicians). Screened participants will be informed about the process and the goals of the research, and that participation is voluntary and that their treatment will not be affected in case they choose to opt out. Active interventions will only be provided for those patients who have given their consent to participate. There will be no transfer of sensitive data from hospital IT systems to the App. Only the data explicitly approved by the patient will be transferred from the App to systems owned by RH. Integrity issues, as well as any new requirements from the data protection regulations, are being continuously monitored by both RH and AF, and scrutinized in the ethics application.

iMedA will be implemented within RH’s current healthcare IT infrastructure. RH and AF have done extensive work to ensure the data storage adheres to all legal aspects including the new 2018 EU directives. iMedA partners have accumulated experience in regulatory and legislative issues, which is seen as a valuable competence for the project, having worked with Sweden's leading legal experts on sorting out the legal landscape related to combining patient data from several sources.

Standards and interoperability

AF has long experience in system wide data analytics and storage, such as building and integrating systems, and will make sure that iMedA follows best practices, e.g., using ICD10 and KVÅ codes. They will also ensure the communication between the AI agent and the App is done in a scalable way. There is no consensus regarding standards for mHealth products or health Apps, but a few initiatives currently stand out. The Personal

Connected Health Alliance[8], also known as the Continua Alliance, is working together with manufacturers, clinicians and other standards organizations to establish guidelines for best practice when developing mHealth products. Another remarkable idea is the Open mHealth Project[9], a collaborative open source initiative that aims to provide support for standardisation of data, storage, sharing, integration and visualization of data. We will follow the guidelines set by these two initiatives as appropriate. In addition, DL will guide integration of iMedA into RH's digital service platform, conduct user tests and evaluate the quality of the digital service that iMedA provides.

Gender equality

The incidence of hypertension is slightly higher in men than women across most European countries[10]. Previous research has shown that men have higher levels of hypertension and lower levels of hypertension awareness than women[11]. A Greek study determined that although hypertension treatment rates did not differ between genders, control rates were lower among females[12]. This suggests that risk factors and optimal intervention strategies may differ between men and women, and must be considered by our AI agent in order to achieve equal efficacy for men and women. Any user studies affiliated with this project will strive to include equal numbers of female and male patients, so that design choices can be equally influenced by both genders. The gender distribution is balanced among senior researchers in the project team with three women and four men identified as responsible for main activities.

Potential and utilisation

The main goal for the hospital is to improve health outcomes and reduce costs related to non-adherence to medication. These costs have been estimated between 9.3 and 11.2 billion SEK in Sweden[13]. Previous intervention studies have reported medium to high effect size in MA[14]. From a resource perspective, it is important to shift patient care from emergency room (hospital), to primary care, and then to home (self-management). During the course of this project we expect to show a significant improvement in MA for the target population due to the combination of PCC and adaptive interventions. Once results show that this is a cost-efficient solution, the extension of iMedA to other patient groups will be considered.

In addition to the cost savings, a large part of the value of our solutions is improved quality of life for patients due to improved MA. We will also assess more general contextual factors and implementation issues of using AI-based solutions like iMedA in healthcare. We are going to apply explorative process evaluation design that includes both questionnaires and interviews. This design is chosen to increase understanding of

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[8] http://www.pchalliance.org/
[9] http://www.openmhealth.org/
[10] https://www.ispor.org/research_pdfs/42/pdffiles/PCV115.pdf
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896734/
[12] https://www.ncbi.nlm.nih.gov/pubmed/18633756
[13] B. Hovstadius and G. Petersson. "Non-adherence to drug therapy and drug acquisition costs in a national population-a patient-based register study." *BMC health services research* 11.1 (2011): 326.
[14] S. Kripalani, Y. Xiaomei, and R. B. Haynes. "Interventions to enhance medication adherence in chronic medical conditions: a systematic review." *Archives of internal medicine* 167.6 (2007): 540-549.

factors that affect an implementation in a given context. In order to draw conclusions about what works and to understand how the implemented intervention has contributed to change, the evaluation also needs to capture the contextual factors that affect implementation and outcomes[15]. Knowledge will be systematized and strategies will be developed for how the new intervention can achieve the goals of the business with increased self-determination among patients and higher satisfaction with care.

AF manages the IT infrastructure for RH, and iMedA will be incorporated into it, adding value to both the company and the region. Both the AI agent for the hospital database and the App can be deployed on a large scale for all patients. The deployment of iMedA will be channelled through RH's digital service platform[16]. AF has over 30 years of experience in transforming the physical world into digital by means of service design, industrial internet, IoT, and advanced analytics. Technical solutions such as iMedA can have a profound impact on general practice and workflow at the hospital, both for practitioners and administrators. Organizational, ethical, and practical issues of large scale implementations will be addressed by complementary project in near future.

Situational analysis

RH is at exceptional advantage worldwide, with large-scale system wide data analysis including a consistent interface to interconnected information systems. iMedA will leverage this infrastructure to truly improve care experience and health outcomes for patients. Today, the missing link is the ability to utilise information to advance PCC, mainly to support patients on a continuous basis after hospital discharge. Since 2008 AF has been designing and maintaining the analysis databases within RH and HH: a revolutionary combination of data sources enabling the hospital to follow patient-level data streams from all levels of the care chain including measurements from primary care, ambulance, emergency care, as well as the traditional EHR's. For all these, the information contains descriptive information around all the clinical activities, i.e., procedures, diagnosis, labs, radiology, medicine, and structured journal input.

There are many Health Apps currently on the market. However, these solutions are usually short-term and often not integrated with the healthcare. We will bridge this gap between personal and public health by leveraging RH's digital services, to become the first region in Sweden to use AI and a common platform to support PCC practices and self-management at home. The main challenge in developing such a holistic solution is the interoperability of data across the public and private sectors. With HU working with triple helix approach for many years, and HH with AF completing large-scale data analysis initiatives, the partners are in a unique position to implement such a solution.

Improving patient health outcomes depends on predicting and understanding MA on an individual level; providing adequate information to doctor and patient in order to mediate a collaborative treatment plan; and supporting the patient at home with adaptive interventions. Individual steps have been undertaken in research, there are however no studies nor commercial products that combine all three aspects using AI agents capable of improving the system over time.

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[15] GF. Moore, et al. "Process evaluation of complex interventions: Medical Research Council guidance." BMJ. 2015; 350:h1258. doi:10.1136/bmj.h1258.

[16] https://projects.invisionapp.com/share/DMDEEK05H

Work packages, budget and schedule

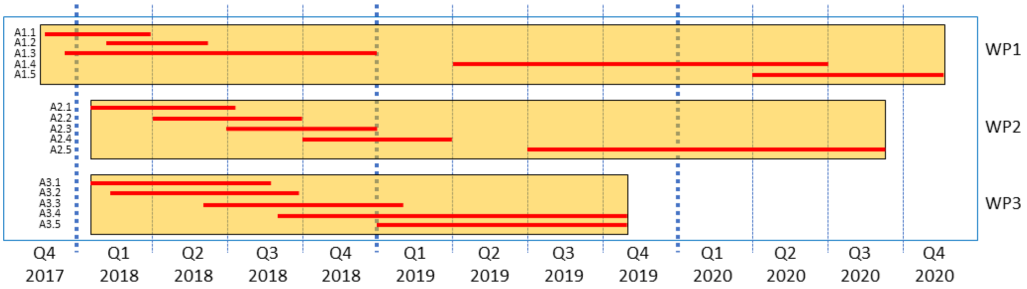
The project is divided into three work packages, plus project management. Each WP includes key activities with appointed leaders (in parenthesis), to better showcase the collaborative aspects of the project. All partners participate in every WP. The project is scheduled for three years, but with lower activity level in the final year.

WP1: Intervention (months **1-36**) **Cost**: 1.2 MSEK
Main Result: Design, implementation and evaluation of the digital intervention.
WP Responsible: Anita Sant'Anna
A1.1 (Marie Olsson-Nerfeldt, KHS): Selection of key target patient groups.
A1.2 (Petra Svedberg, CVHI): Study design and application for ethical approval.
A1.3 (Anita Sant'Anna, CAISR): Compilation of literature on intervention strategies for hypertensive patients and analysis of implementation feasibility within iMedA project.
A1.4 (Markus Lingman, HH): Intervention implementation and coordination.
A1.5 (Petra Svedberg, CVHI): Investigation of key acceptance factors for iMedA.

WP2: AI Agent Development (months **3-33**) **Cost**: 1.7 MSEK
Main Result: iMedA AI agent. **WP Responsible**: Slawomir Nowaczyk
A2.1 (Slawomir Nowaczyk, CAISR): Comprehensive representation of patient data.
A2.2 (Anita Sant'Anna, CAISR): Identification of groups of similar patients.
A2.3 (Thomas Wallenfeldt, AF): Implementation of medication adherence prediction.
A2.4 (Markus Lingman, HH): Selecting intervention strategies for individual patients.
A2.5 (Joel Sanden, DL): Improving iMedA based on patient feedback & follow-up data.

WP3: User experience (months **3-24**) **Cost**: 1.5 MSEK
Main Result: iMedA App and Dashboard. **WP Responsible**: Joel Sanden
A3.1 (Petra Svedberg, CVHI): Defining how to present information on the dashboard.
A3.2 (Markus Lingman, HH): Design of doctor-patient interactions iMedA will support.
A3.3 (Joel Sanden, DL): Creating user interactions for iMeda intervention App.
A3.4 (Thomas Wallenfeldt, AF): System integration and deployment within hospital IT.
A3.5 (Slawomir Nowaczyk, CAISR): Integrating iMeda App with iMedA AI agent.

WP4: Project Management (**1-36**) **Cost**: 0.3 MSEK **Responsible**: Slawomir Nowaczyk
Description: Project management, progress monitoring and dissemination of results.
Main Result: A smoothly running project that achieves the goals.



Total budget for iMedA is 4.7 MSEK, of which we are seeking 3 MSEK (63.8%) from Vinnova, and project partners are contributing 1.7 MSEK. Co-financing from HU and RH is approximately 30%, and co-financing from AF is 60%. The planned distribution of **Vinnova grant** and *own commitment* across partners is presented in the table below:

	Year 1	Year 2	Year 3
HU	**0.8** + *0.3*	**0.8** + *0.3*	**0.2** + *0.1*
RH	**0.3** + *0.1*	**0.3** + *0.1*	**0.1** + *0.1*
AF	**0.2** + *0.3*	**0.2** + *0.3*	**0.1** + *0.1*